Themed Issue: Role of Biomarkers in Drug Development
Guest Editors - Brian P. Booth and Jogarao V. Gobburu

Commentary: Where and How Could Biomarkers Be Used in 2016

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ABSTRACT

Since the beginning of the human genome project there has been considerable speculation about how this resource and the knowledge creation it enabled would change therapeutic discovery, development, and delivery. As the project neared completion, considerable claims and predictions were made about the changes that soon would be forthcoming. Many of these early predictions failed to materialize, however, leading to further speculation about the reasons, including the role of the pharmaceutical industry in realizing the promise of "genomic medicine." During this same period, considerable strides were made in other areas of molecular biology and medicine, and in response scientific thinking naturally evolved. Researchers and regulators moved from a genotype-centric view to a view that all biomarkers are potential tools to improve drug development and therapeutic decision making. Molecular biology is now seen as encouraging more "personalized medicine"—the closer alignment of biological information (derived from molecular diagnostics) and therapy selection. Meanwhile, there are growing concerns that increasing expenditures in pharmaceutical research and development are not sustainable and not reaping sufficient gains for shareholders or society at large. Thus, there is new speculation about how biomarkers, personalized medicine, and the industry will interact and create value for patients. This overview seeks to explore the issues driving pharmaceutical productivity and the likely contribution of biomarkers in the future.

KEYWORDS: Pharmaceutical productivity, biomarkers, molecular diagnostic, drug discovery, innovation

INTRODUCTION

There are several important issues driving both optimism and pessimism surrounding the pharmaceutical industry. Some people argue that the large investment needed to support research and development (R&D) is not providing the necessary returns, as defined by the combination of clinically differentiated medicines and an increase in shareholder value. Others contend that with the human genome sequence in hand, drug discovery and development will become simpler, faster, cheaper, and more predictable. Despite the range of opinions, many agree that the evolution of molecular medicine, coupled with the discovery and clinical application of new biomarkers, will play a significant role in reshaping science and business. This article will explore the issues driving pharmaceutical productivity and the likely contribution of biomarkers in the future.

First, what is a biomarker? How can the application of biomarkers in clinical development affect clinical practice? Biomarkers are an objective measure or evaluation of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic or other health care intervention. They may or may not be dynamically modulated, and they can increase our understanding of drug metabolism, action, efficacy, and safety. They can be examined to facilitate response prediction, expand the molecular definition of disease, and provide information about the course of disease. This broad definition includes all diagnostic tests, imaging technologies, and any other objective measures of a person's health status. In short, biomarkers span a broad sector of human health care and have been around since the understanding of human biology, diseases, and therapy interventions began to evolve.

So, why is so much attention being paid to biomarkers today? Genetics, genomics, proteomics, and modern imaging techniques and other technologies allow us to measure more markers than before. In addition, we have a greater understanding about disease pathways, the protein targets we are addressing medicinally, and the pharmacologic consequences of our medicines. We are therefore able to conclude that the application of biomarkers in the clinic will yield richer knowledge that will allow us to better understand and position drugs in the market. Thus, we anticipate a steady and exciting evolution of the drug development process and the practice of medicine.

For the purpose of this overview, rather than asking how things *will be* at defined future moments (eg, in 5-10 years we will know the susceptibility factors for common illnesses, by 2020 doctors will be prescribing gene-based designer drugs to their patients and gene therapy will be the

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standard of care) we will ask how things *could be*. So how could things be in 10 years with respect to biomarkers and drug development? Better? Worse? The same? Clearly, everyone—society, industry, academia, health care providers, and patients—wishes things to be better. Thus, we focus on this question: What could a better world look like, and how could it come to exist?

Experience in research tells us, ultimately, that all the innovation and progress we achieve with biomarkers will be driven and limited by science, and science, in turn, is driven and limited by (1) technology, and (2) creative minds seeing new ways to understand and apply new knowledge. While science is the paramount factor, we recognize the other forces—for instance, market pulls, regulatory requirements, economic incentives, and public perceptions—that play a significant role in how drug development is changed by biomarkers. We must assess these factors in relation to where we are today and how we arrived there before we can consider where we could go in the future.

The Past Becomes the Present

> The past is never dead. It isn't even past. William Faulkner

Today in the pharmaceutical industry, higher investments in R&D are providing lower than anticipated returns. R&D for new medicines is more costly, yet the number of new molecular entities (NMEs) coming out of the pipeline is declining. There is a tendency to correlate productivity with spending and to measure productivity in terms of quantity rather than quality. Comparing dollars invested today with performance of medicines in the market today, however, does not accurately measure current productivity, since the process of discovering new medicines is long (10-15 years), expensive ($0.8-$1.5 billion), and risky (10% success following first dose in humans).[1] We postulate that the real measure of productivity should be impact on health. While there may be fewer NMEs submitted for regulatory approval, the actual value these new medicines are creating in long-term health gains may be greater than that of older medicines. Moreover, although the speed of regulatory review has increased, there is considerable concern that the current climate surrounding drug safety will lead to greater costs and more delays. Add to this the distraction and value destruction of mergers and acquisitions, and it is not surprising that drug development is seen as being in decline. Furthermore, the predicted gains that were to be derived from the human genome sequence have not materialized. What created and perpetuates this situation? Several important factors have either directly confounded or have been perceived to negatively affect R&D and productivity, in general.

First, significant merger and acquisition activities have dominated the industry in recent years. Rather than aiming to increase the overall investment in R&D, these transactions have focused on enhancing the size and value of the product pipeline. Of greater importance, we have found that it can take 2 to 4 years for the newly merged company to begin to deliver consistent R&D productivity, as measured by sustainable delivery of NMEs entering the clinic. As a consequence, when the 2 to 4 year gap has moved to the point where products would have been expected to be entering the market, the real negative impact of the merger and acquisition activity is felt (Figure 1). Clearly, these types of activities destroy innovation and overall value to the consumers and shareholders.

Second, during the 1990s the industry was making an important transition on the discovery front. With knowledge of the human genome growing and with the implementation of combinatorial chemistry and high-throughput screening, several issues arose: (1) the large number of protein targets emerging required rapid interrogation by chemical entities via high-content screening; (2) these combined efforts led to an exponential increase in the generation of "data points" coming from the screens; and (3) to extract further information from the large amount of data and to begin to address druglike properties in the filtering processes, the development and application of higher-throughput absorption, distribution, metabolism and excretion assays was required. These 3 drivers required significant internal and external pharmaceutical investment and clearly affected the short-term productivity of NMEs. While productivity as measured by data points increased, success did not, owing to an overall lack of investment in target validation efforts (efforts to demonstrate that the protein of interest contributes to the disease and that modulating the activity of the protein will have the desired impact on disease progression).

Third, many people believe that during the past 5 to 10 years, the industry has been introducing non-innovative "me too" drugs as opposed to "first in class" medicines into

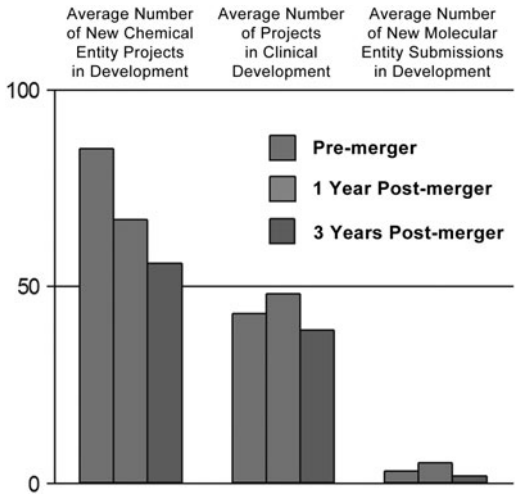

Figure 1. The impact of mergers on research and development.

the health care system. While this can be debated by the burden of proof, it is worth noting that "me too" and "me better" drugs play an important role in health care management. Most medicines have been shown to be effective in approximately 30% to 50% of the disease population that they address. This means that many individuals do not gain a direct benefit from their therapeutic regimen. In most cases, this does not threaten their lives. The fact that a physician can move a patient to another drug for the same indication provides hope for that patient. While this trial-and-switch approach is costly and causes an individual to suffer from symptoms for a longer time, in the end having multiple options can provide the desired outcome. Learning how to apply biomarkers to this paradigm will allow us in the future to better identify those individuals that will benefit from the multiple classes of drugs by addressing their indications.

Another important point is the perception of innovation. Clearly, discovering medicines that address unmet medical needs represents novel breakthroughs. However, evolving current medicines to enhance drug-like properties, efficacy, tolerability, and convenience represents important innovations as well. Consider the case for the interferon alpha 2a, which is the gold-standard therapy for hepatitis C. By pegylating this protein, we were able to extend the exposure of the drug, thereby promoting highly efficient viral clearance. Was this innovative? If you asked the patients and providers, they would respond yes.

Fourth, in the past 10 to 15 years, we began to move away from developing drugs targeting pathogenic organisms and acute human indications, and to move toward developing drugs targeting diseases of aging and those associated with the complex interplay between genetics and the environment. These polygenic disorders include cardiovascular disease, type 2 diabetes, arthritis, and cancer. The critical issue became identifying disease pathways and in particular those genes that play a crucial role in contributing to disease susceptibility, onset, and progression. It was believed that having knowledge of the complete set of human genes would allow us to rapidly gain these understandings and that the targeted, molecular-based new drugs emerging from these endeavors would successfully address these important diseases. While concepually correct, the important yet overlooked fact is that the translation of a DNA sequence into knowledge about gene function and dysfunction relating to a human disease is a long-term endeavor.

Often, the perceived delay is mistakenly assumed to arise from industry reluctance to stratify patients and thus reduce markets. In addressing this issue, we must ask: Were the expectations that the completion of the human genome sequence would have an immediate impact on drug development reasonable? Given that it takes about 12 years to discover and develop a new drug and that drugs coming onto the market today would have been well into clinical trials when the draft sequence was published in 2001, was it reasonable to expect the sequencing to have affected today's new products? How could this admittedly vast quantity of data, for which biological significance largely remains to be determined, have been expected to changed things so rapidly? But what was created at the time was vital.

The initial significant change ushered in by the genome sequence was the creation of new possibilities. Now that we have the technologies, the informatics platforms, and a growing understanding of the molecular basis of human diseases, we must find ways to enhance the quality and value of the medicines we are attempting to invent. The high industry attrition rates in phase I (50%) and II (70%) must be addressed. To address the phase I attrition, we believe that identifying and testing multiple lead series in the clinic and early in vitro/in vivo/in silico assessment of compound toxicity will enhance the quality of the compounds entering phase II. To address the phase II attrition, we believe our efforts to identify higher-quality drug targets and early evaluation and understanding of human diseases and pharmacology in the clinic will help. The contribution of biomarkers to improving these and other steps in drug development will depend on their relevance to need, and many biomarkers may have multiple purposes (Figure 2).

There has been vast experience with markers such as cholesterol, glucose, and triglycerides, so these types of markers are readily employed in development. And we have a growing number of markers that aid therapy choice, such as Her 2, thiopurine methyltransferase (TMPT), and p450 metabolizing enzymes. But only Her 2 is specified in a drug label and used routinely in clinical practice. TMPT testing is used by some clinical organizations before administering thiopurine drugs,[2] but labeling does not require testing, reimbursement policy varies,[3] and many groups continue to

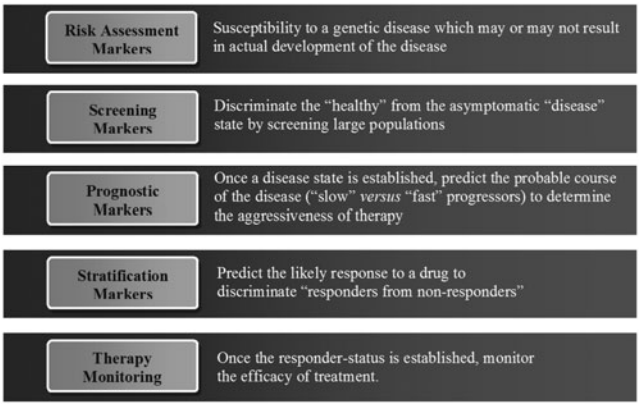

Figure 2. Novel diagnostics markers: spanning the health care continuum. Source: Centre Watch 2001 based on analysis of 22 mergers 1988-1999, including AstraZeneca, Ciba Geigy & Sandoz, Pharmacia & Upjohn and Glaxo & Wellcome.

rely on existing treatment-monitoring methods. While drug-metabolizing enzyme variations have been known for decades, we are only now developing the tools and necessary clinical associations to allow for testing prior to prescribing or altering a drug dose. This pharmacogenomic knowledge is currently being translated by much-needed clinical research. For example, the Mayo Clinic in Minnesota is studying the relation between psychotropic drug dose, response, and patient metabolic state, as measured by the Roche AmpliChip CYP450. The first step of this collaboration is to co-develop a prototype information technology–enabled system that will offer drug selection and dosing information for a broad range of psychotropic therapeutics based on patient test results.[4] As prospective studies in other therapeutic areas produce results, patients elsewhere could also soon benefit from reduced side effects and increased efficacy through knowledge of metabolic status.

When other biomarkers will prove to be clinically useful will depend on several factors: disease characteristics and therapeutic options, therapeutic window, toxicology profile, and target variations or other variants in the pathway that directly influence drug action. For indications such as oncology where both specificity and speed may make a substantial difference in outcome, biomarkers will likely play a greater role clinically. Payers, however, are questioning the cost-effectiveness and clinical utility of some new tests coming to the market, typically calling for more prospective data.[5] It must be remembered that it took decades of research to understand markers such as cholesterol and prostate serum antigen, and the clinical implications of their varying values. In many instances we are still learning.[6] Thus, biomarkers in and of themselves are not novel; the question is, How do we more quickly discover and discern clinically meaningful markers that provide greater predictability in development and treatment?

Many efforts are under way. Serious discussions are beginning about clinical need and practicality with regard to biomarkers and segmenting disease—including asking when and where it makes biological and clinical sense to seek and apply novel biomarkers. Most pharmaceutical companies today routinely bank samples to refer back to in the event of unexpected results during clinical development. Moreover, many labs, from academia to pharmaceutical and diagnostic industries, are actively seeking new disease-related markers. As there is greater realization that not all patients respond the same way to a drug, it is easier to see how alleged "me too" drugs address real patient needs, but identifying potential responders and nonresponders remains a difficult task. The US Food and Drug Administration is working with all stakeholders to develop guidance[7] with regard to biomarkers as well as to initiate public-private consortia and other projects to support the critical path to improving innovation.[8] Thought is evolving on developing business models that consider differences in diagnostic and pharmaceutical development, manufacture, product life cycle, and reimbursement structures to enable co-development of drugs and diagnostics when and where it makes sense.

While the high expectations have not been met, much progress has been made. Many stakeholders are committed to improving drug development and health care through application of new biomarker technologies and knowledge as well as new policies to facilitate needed regulatory and reimbursement reforms.

So what is needed today to allow for change tomorrow? The most difficult step involves changing the way some things are done now.

THE FUTURE

> The important thing is this: To be able at any moment to sacrifice what we are for what we could become. Charles DuBois

The future of medicine will depend upon considering the following today:

1. The public sector must rethink the mix of basic, individual investigator–initiated and translational, team-led, multicenter research in tax-supported research portfolios. Without well-designed efforts to develop general knowledge about the molecular history of diseases, progress with biomarkers will be very slow.
2. How biomarkers are perceived and understood and how some scientists and investigators are trained will be important. More individuals who can think about genetics in terms of human health and complex disease—who apply genetics to quantitative traits—are needed. As our understanding of medical genetics grows to include complex disease as well as monogenic disorders, we need to tailor professional curriculum appropriately. While the model of care for rare genetic disorders works well to address the needs of patients and families contending with monogenic disease, it is unlikely to translate to routine care of common disorders. Thus, suitable new effective and efficient models of incorporating genetics into broader medical care must be created. Furthermore, biomarkers must be clinically contextualized based on function, not analyte.
3. To enhance the use of biomarkers, we need to understand how they become accepted and adopted today so we can create better processes for their assessment. Generation of prospective data will be necessary for validation and demonstration of clinical utility, but how such studies are supported will depend on incentives and the ability to capture the

value created. Current reimbursement structures and commercial models do not support many aspects of biomarker innovation.

4. As the foundation of molecular knowledge grows, regulators, industry, and society will have to change the way risk and benefit are quantified and contextualized. If better predictors are found, they must be allowed to replace existing methods and technologies, not simply be added on.
5. Industry will need to rethink risk in its development portfolio as the ability to parse and predict human variation in disease state and therapy response grows. If we are given information that allows better prediction and an appropriate regulatory environment to exploit that knowledge, attrition and development costs should decrease in time (although they are surely likely to increase in the short term).
6. To provide incentive for biomarker innovations, appropriate business models must be adopted. If a targeted therapy requires the clinical use of a biomarker, the linked product must be valued accordingly. Currently, diagnostics are undervalued by most reimbursement structures.[9] Additionally, payers will need to value targeted drugs.

So, if we begin these changes today, and in particular put significant experimental medicine research efforts in place, where could biomarkers be in drug development in 10 years?

From any single portfolio in 2016, while most attempts will have already failed, a few molecules developed against targets being brought into development today will be in clinical trials. In some cases, variations in the target or pathway will have been identified during preclinical development—either in-house or by other groups—that will generate hypotheses of how the drug might behave differently depending on the variant. Testing of the hypothesis will then be accomplished by ensuring that each group is represented in the trial population. This will likely increase (not decrease) the trial size and potentially lengthen the time to recruit individuals.

If the drug shows efficacy, results from the hypothesis testing will inform developers and regulators about its appropriate use, add value to the patient population, and contribute to general knowledge about perturbation of the disease via that mechanism.

For many of the targets we are selecting in 2016, we will know whether and how many variant forms exist and, in some instances, whether the variation has anything to do with disease risk, development, or prognosis. Additionally, for a few of these targets we will be able to hypothesize about and test for variation in drug action in models preclinically, enabling better selection of clinical candidates. This will allow us to stratify patients prior to clinical trial enrollment in instances where the preclinical work supports it. Stratification will require availability of the requisite assay. If the biomarker is accepted, it should follow the standard steps during the development process and regulatory review. If, however, the marker's clinical utility remains in question, the trials will need to be designed to test its use as well as the efficacy and safety of the drug.

Under either scenario, the developer will have enabled clinical differentiation of its product; the regulator will have better science from which to base decisions, making the process clearer and faster; and patients and physicians will have better information to use when considering individual risk and benefit. Payers will have information to support providing appropriate patient access to the drug. In essence, we will have a more personalized approach to patient care that is more certain and effective.

We look forward to a brighter future for patients, the industry, and society.

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